



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Maria Gabriella Brasca et al.

Examiner: Charanjit Aulakh

Serial No: 10/539,145

Art Unit: 1625

Filed: May 4, 2006

Docket: 17700 (PC27545A)

For: SUBSTITUTED PYRROLO-PYRAZOLE DERIVATIVES AS
KINASE INHIBITORS

Confirmation No: 2225

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Marina Ciomei declares that:

1. she has a degree in biological sciences (cum laude) from the University of Pisa, granted in 1980;

2. she has a PhD (cum laude) from the University of Pavia, granted in 1984;

3. she has conducted research in the pharmaceutical field since 1984;

4. she has been Associate Director of Cell Biology Signal Transduction, at Nerviano

Medical Sciences, Milan since 2004;

5. she has worked in collaboration with the applicants of the above-identified application in testing compounds they developed for activity as protein kinase inhibitors;

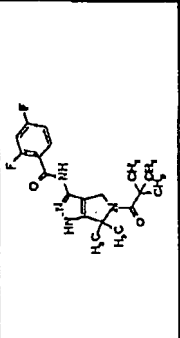
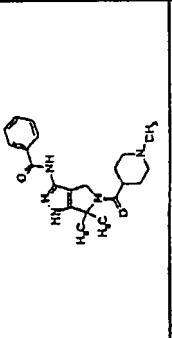
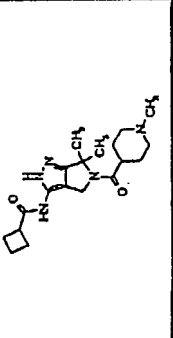
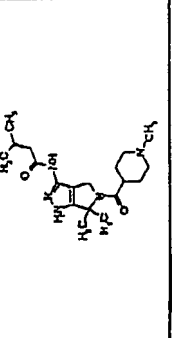
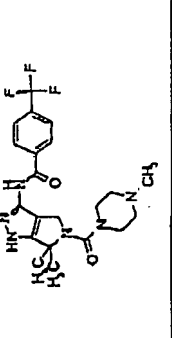
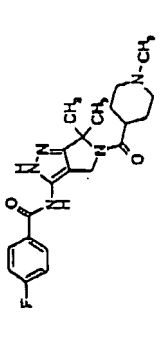
6. she conducted tests or had tests conducted under her direction wherein compounds within the scope of formula (Ia) and (Ib) were evaluated for their activity as protein kinase inhibitors. Specifically, the compounds in the Table below were tested to determine their Cdk2/Cyclin A inhibitory activity in accordance with the procedure set forth at Page 29, line 10 et seq. of the specification of the above-identified application. The results of evaluations are summarized in the Table below:

TABLE

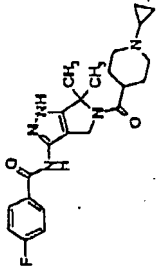
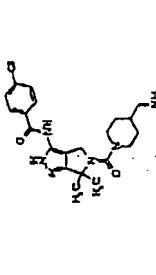
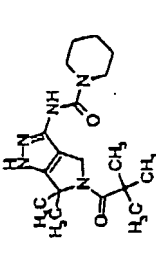
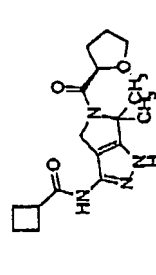
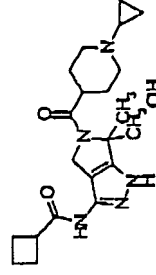
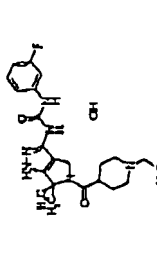
Specification Reference	Structural Formula	Chemical name	CDK2/A (IC50 microMolar)
A01-M1-B28		Pyrido[3,4-c]pyrazole-5(1H)-carboxamide, N-ethyl-3-[(4-fluorobenzoyl)amino]-4,6-dihydro-6,6-dimethyl-	0.20
A01-M1-B01		Benzamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-4-fluoro-	0.03
A13-M1-B01		Cyclobutanecarboxamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-	0.01
A06-M1-B01		Benzamide, 4-chloro-N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-	0.05
A07-M1-B01		Benzamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-4-(trifluoromethyl)-	0.19
A12-M1-B01		Butanamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-3-methyl-	0.02

A01-M1-B08	
A01-M1-B09	
A10-M1-B01	
A06-M1-B08	
A04-M1-B08	
A14-M1-B01	

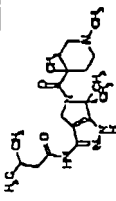
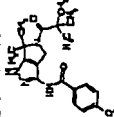
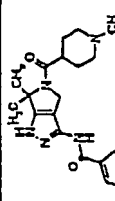
Benzamide, 4-fluoro-N-[2,4,5,6-tetrahydro-6,6-dimethyl-5-[(4-methyl-1-piperazinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.04
Benzamide, 4-fluoro-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-(1-piperidinylcarbonyl)pyrrolo[3,4-c]pyrazol-3-yl]-	0.06
2-Thiophenecarboxamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-	0.02
Benzamide, 4-chloro-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(4-methyl-1-piperazinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.04
Benzamide, 2,4-difluoro-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(4-methyl-1-piperazinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.04
Cyclopropanecarboxamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-	0.11

A04-M1-B01	
A30-M1-B03	
A13-M1-B03	
A12-M1-B03	
A07-M1-B08	
A01-M1-B03	

Benzamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-2,4-difluoro-	0.06
Benzamide, N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(1-methyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.02
Cyclobutanecarboxamide, N-[2,4,5,6-tetrahydro-6,6-dimethyl-5-[(1-methyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.01
Bulanamide, 3-methyl-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(1-methyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.01
Benzamide, N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(4-methyl-1-piperazinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-4-(trifluoromethyl)-	0.05
Benzamide, 4-fluoro-N-[2,4,5,6-tetrahydro-6,6-dimethyl-5-[(1-methyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.02

A01-M1-B05	
A06-M1-B16	
A28-M1-B01	
A13-M1-B14	
A13-M1-B05	
A27-M1-B04	

Benzamide, N-[5-[(1-cyclopropyl-4-piperidinyl)carbonyl]-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-4-fluoro-	0.07
Benzamide, N-[5-[[4-(aminomethyl)-1-piperidinyl]carbonyl]-2,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-4-chloro-	0.04
1-Piperidinecarboxamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-	0.23
Cyclobutanecarboxamide, N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[[[(2R)-tetrahydro-2-furanyl]carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.04
Cyclobutanecarboxamide, N-[5-[(1-cyclopropyl-4-piperidinyl)carbonyl]-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-, monohydrochloride	0.02
Pyrrolo[3,4-c]pyrazol-3-amine, 5-[[[1-ethyl-4-piperidinyl]carbonyl]-N-[[[(3-fluorophenyl)amino]carbonyl]-1,4,5,6-tetrahydro-6,6-dimethyl-, monohydrochloride	0.01

A12-M1-B21	
A31-M1-B01	
A17-M1-B03	

Formic acid, compd. with 3-methyl-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(1,4-dimethyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]butanamide (1:1)	0.02
Benzamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]-4-[(1-methyl-4-piperidinyl)oxy]-	0.08
Benzamide, 3-phenoxy-N-[1,4,5,6-tetrahydro-6,6-dimethyl-5-[(1-methyl-4-piperidinyl)carbonyl]pyrrolo[3,4-c]pyrazol-3-yl]-	0.04

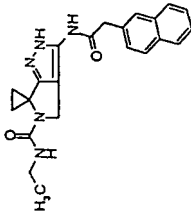
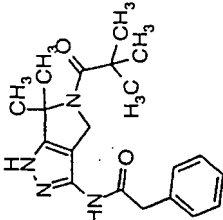
Specification Reference	Structural Formula
A01-M2-B28	
A01-M2-B01	
A01-M2-B08	
A01-M2-B05	
A01-M2-B03	
A06-M2-B04	

Chemical name	CDK2/A (IC50 microMolar)
Spiro[cyclopropane-1,6'-(5'H)-pyrrolo[3,4-c]pyrazole]-5'-carboxamide, N-ethyl-3'-[(4-fluorobenzoyl)amino]-1',4'-dihydro-	0.30
Benzamide, N-[5'-(2,2-dimethyl-1-oxopropyl)-4',5'-dihydrospiro[cyclopropane-1,6'-(2'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-4-fluoro-	0.025
Benzamide, N-[4',5'-dihydro-5'-[(4-methyl-1-piperidinyl)carbonyl]spiro[cyclopropane-1,6'-(2'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-4-fluoro-	0.23
Benzamide, N-[5'-[(1-cyclopropyl-4-piperidinyl)carbonyl]-4',5'-dihydrospiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-4-fluoro-	0.06
Benzamide, N-[4',5'-dihydro-5'-[(1-methyl-4-piperidinyl)carbonyl]spiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-4-fluoro-	0.03
Benzamide, 4-chloro-N-[5'-[(1-ethyl-4-piperidinyl)carbonyl]-4',5'-dihydrospiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-	0.06

A10-M2-B03	
A12-M2-B03	
A27-M2-B01	
A12-M2-B01	
A13-M2-B03	
A04-M2-B04	

2-Thiophenecarboxamide, N-[4',5'-dihydro-5'-[(1-methyl-4-piperidinyl)carbonyl]spiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-	0.02
Butanamide, N-[4',5'-dihydro-5'-[(1-methyl-4-piperidinyl)carbonyl]spiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-3-methyl-	0.02
Spiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-amine, 5'-(2,2-dimethyl-1-oxopropyl)-N-[[3-(fluorophenyl)amino]carbonyl]-4',5'-dihydro-	0.15
Butanamide, N-[5'-(2,2-dimethyl-1-oxopropyl)-4',5'-dihydrospiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-3-methyl-	0.003
Cyclobutanecarboxamide, N-[4',5'-dihydro-5'-[(1-methyl-4-piperidinyl)carbonyl]spiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-	0.003
Benzamide, N-[5'-[(1-ethyl-4-piperidinyl)carbonyl]-4',5'-dihydrospiro[cyclopropane-1,6'-(1'H)-pyrrolo[3,4-c]pyrazol]-3'-yl]-2,4-difluoro-	0.01

TABLE

Specification Reference	Structural Formula	Chemical Name	CDK2/A (IC50 microMolar)
A48-M2-B28		Spiro[cyclopropane-1,6'-(5'H)-pyrrolo[3,4-c]pyrazole]-5'-carboxamide, N-ethyl-1',4'-dihydro-3'-[(2-naphthalenylacetyl)amino]	0,022
A47-M1-B01		Benzeneacetamide, N-[5-(2,2-dimethyl-1-oxopropyl)-1,4,5,6-tetrahydro-6,6-dimethylpyrrolo[3,4-c]pyrazol-3-yl]	0,004



7. all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not.

Dated: 28 June 2007

Marina Ciomei
Marina Ciomei